REMARKS

This submission is in response to the Office Action mailed March 11, 2003. New claims 6-24 have been added. Support for the new claims can be found in the specification as follows: **claim 6**-page 12, line 26, to page 14, line 20; **claims 7-8**-page 9, lines 20-26; **claims 9-11**-page 6, lines 26-29, and Example 1; **claims 12-17**-page 6, line 29, to page 7, line 5, and Examples 3 and 4; and **claims 18-24**-page 7, lines 6-19, and Example 3. Reconsideration of the above identified application, in view of the following remarks, is respectfully requested.

Claim Rejections Under 35 U.S.C. §102(b)

Claim 1 stands rejected as anticipated by Li et al., Proc. Natl. Acad. Sci. U.S.A. 1997; 94:73-78 ("Li"). The Examiner alleges that Li discloses a method for identifying a compound that inhibits a protein-protein interaction, by identifying surface binding pockets for ligand binding according to the same method as presently claimed. This rejection is respectfully traversed.

Contrary to the method of the present claims, Li discloses a computer-based strategy for identifying compounds that bind to a critical binding pocket on the surface of the CD4 T cell receptor. This critical binding pocket is defined as the site where the CD4 receptor interacts (i.e., binds) with the MHC II antigen on the antigen-presenting cell, *e.g.*, a ligand-binding site. Li used computer algorithms (DOCK and APROPO) to identify sites on CD4 that were putative ligand-binding sites (page 74, column 1). Two of theses sites, referred to as the FG and CC' loops located in the CD4 D1 domain, were proposed to form a cavity that directly interacts with

the MHC II antigen. Li then used computer screening to identify non-peptide ligands for this binding pocket based on their shape complementarity and interaction energy with the binding pocket.

In contrast to Li, the present invention claims a method of identifying compounds that bind to surface cavities that are proximal to the functionally critical site (i.e., the site that is involved ligand binding or dimerization, etc.) of a target protein. This proximal site is referred to as an allosteric site. Binding of compounds to the allosteric site modulates the interactions between the functionally critical site and other proteins, thereby affecting its function by allosteric modification. According to the invention, the allosteric cavity is at a distinct location from the functionally critical site.

Since claim 1 calls for identifying a proximal cavity to the functionally critical site, and this feature is not taught or suggested in the reference, withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. §112-Second Paragraph

Claim 1 also has been rejected as indefinite for reciting the term "accommodated." The Examiner contends that it is unclear what criteria of the functional groups of a compound are used to determine if it can be accommodated by an allosteric cavity.

The term "accommodated" is well-defined in the specification. The Examiner's attention is respectfully directed to page 5, lines 21-23 of the specification, which states that "The

parameters for identifying such functional groups and compounds include size, charge and hydrophobicity/hydrophilicity characteristics," and to page 11, lines 17-24, which discloses that "Such parameters include at least one and preferably more than one of the following: the volume and dimensions of the cavity...; the electrostatic properties....and/or the chemical properties, *i.e.,* hydrophobicity/hydrophilicity." The specification further elaborates on these criteria at page 11, line 25 to page 14, line 2. For example, the specification teaches that mapping of electrostatic and chemical properties can be achieved by identifying atoms (using computer programs such as GENSITES and SPHGEN) that are capable of forming hydrogen bonds. The specification also teaches that functional groups that can be accommodated by the cavity must have electrostatic and chemical properties which would "result in forces that attract the functional group to the interior of the cavity rather than repelling forces which wold inhibit or prevent the functional group from occupying the interior of the cavity" (page 12, lines 18-21). The specification further teaches that computer programs such as LUDI and CAVEAT can be used to identify the functional groups which can be accommodated by the cavity.

In view of the above, it is respectfully asserted that the term "accommodate" meets the definiteness requirement of the law. Accordingly, withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. §112-First Paragraph

Claim 1 stands rejected for lacking enablement. The Examiner asserts that claim 1, while being enabled for a method of identifying a compound that modulates interaction between a TNF

receptor and a modifier, is not enabling for identifying a compound that modulates the interaction between any protein and its modifier(s). The Examiner further contends that it would require undue experimentation to identify compounds for target proteins other than the TNF receptor, since protein crystallization, used by the present inventors to evaluate the topography of the TNF receptor to practice the claimed method, is an unpredictable art. The Examiner reasons that crystallization of any protein prior to evaluation would require undue experimentation.

To support his position, the Examiner cites an excerpt from a textbook about protein crystallography ("Drenth"), and an article from *Science* magazine published in November 2002. The Drenth excerpt states that crystallization is unpredictable and requires trial-and-error analysis, while the *Science* article discusses the technical barriers that have impeded the identification of structural mapping of proteins by crystallization.

This rejection is respectfully traversed.

First, it is asserted that the specification exemplifies, and therefore enables, identification of compounds that modulate interactions between the CD4 receptor and the MHC/antigen/TCR complex (Example 3), and between the enzyme β-lactamase and its substrate, β-lactam (Example 4). Hence, contrary to the Examiner's contention, claim 1 is enabled for more than the TNF-α receptor.

Further, in contrast to the Examiner's opinion, identification of functional critical sites (and allosteric sites proximal to the functional sites) does not necessarily require knowledge of the crystal structure of the target protein. Pages 10-11 of the specification teaches that identification of functional sites and allosteric cavities can be achieved using crystal **or** NMR

imaging, **or** microcalorimetric analysis from thermodynamic studies, **or** mutation analysis, **or** by protein, peptide or peptidomimetic mapping of the target protein **or** by identifying CDRs on the target protein structure, **or** by computer modeling.

Moreover, such techniques are well known to those of ordinary skill in the art. In fact, Li, cited by the Examiner and discussed above, used an approach involving theoretical analysis based on computer-based algorithms (*e.g.*, APROPOS, DOCK and DELPHI) to identify binding pockets (page 74, column 2). Li further states that following identification of a critical site, computer screening to generate non-peptide ligands took less than a month of effort (at page 77, first column). The specification also refers to references to algorithms and other methods to identify cavities (page 10, line 29, to page 11, line 11).

In addition, protein structures can be predicted from the primary amino acid sequences using computer-based *de novo* or *ab initio*[1] methods. Such techniques were well-known in the art at the time of filing the application, as demonstrated, *e.g.*, by Fetrow et al., *J. Mol. Biol.* 1998; 281; 949-68; 14: 196-205 (see pages 950, column 1, bottom; and column 2, bridge paragraph, and ; Pazos et al., *J. Mol. Biol.* 1997; 271:511-23 (see page 512, second column, second paragraph, page 515, bridging paragraph, and page 520, first column, third paragraph); and Cui et al., Proteins: Structure, Function and Genetics 1998; 31:247-57 (all attached as Exhibits 1-3, respectively).

Further, despite the Examiner's contention that protein crystallization is unpredictable, the

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[1] *ab initio*-"from first principles"-relies on thermodynamic laws and predict secondary structure then tertiary structure.

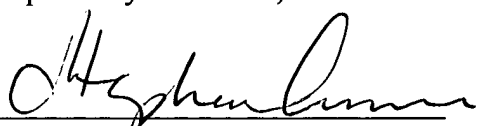
fact is that numerous proteins have been crystallized to date (3547 crystal entries from 2526 biological macromolecules as of 1998-National Institute of Science and Technology-see Exhibit 4), and methods employing sequence and structural alignment with the "known" proteins are powerful predictors of the structure of uncrystallized proteins (knowledge-based method). See for example, Koonin et al. *Curr. Opin. Struct. Biol.* 1998; 8:355-63 (see pages 359-361), attached as Exhibits 5. In addition, the computer-based methods drastically reduce the timing for prediction when compared to e.g., protein crystallization. The Cui article, attached as Exhibit 3, indicates prediction of the solvent-accessible surface area of the N-terminal region of the 434 repressor protein in 0.115 ***seconds*** (see page 247, column 1, second paragraph and page 250).

In view of the foregoing, Applicants assert that the present claims are enabled according to the *Wands* factors. The present specification contains all of the information that would be needed by a person of ordinary skill in the art to practice the invention defined by claim 1. Accordingly, withdrawal of this rejection is respectfully requested.

Therefore, in view of the above remarks and references, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,



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